POLICY AND COMMUNICATIONS BULLETIN
THE CLINICAL CENTER

Medical Administrative Series

M80-3 (rev.) 29 October 1999

MANUAL TRANSMITTAL SHEET

SUBJECT: The Use of Investigational Drugs in Patient Care

1. Explanation of Material Transmitted: This policy was reviewed by the Medical Executive Committee on 19 October 1999 and approved with no substantive changes.

2. Material Superseded: MAS No. M80-3 (rev.), dated 17 June 1997

3. Filing Instructions: Pharmacy Section

   Remove: No. M80-3 (rev.), dated 17 June 1997

   Insert: No. M80-3 (rev.), dated 29 October 1999

DISTRIBUTION

Physicians, Dentists and Other Practitioners Participating in Patient Care

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SUBJECT: The Use of Investigational Drugs in Patient Care

PURPOSE

The purpose of this issuance is to consolidate the various policies and procedures pertaining to investigational drugs.

DEFINITIONS

1. An investigational or new drug is any drug that has not yet been released for general use and has not been cleared for sale in interstate commerce by the Food and Drug Administration (FDA). Although an investigational drug may be a new chemical substance, it may also be one of the following (Ref: Title 21 Code of Federal Regulations, part 310.3):

   a. An old or approved drug proposed for a new use.
   b. A new combination of two or more old drugs.
   c. A combination of old drugs in new proportions.
   d. A new dosage form or method of administration.
   e. A drug that contains a new component such as a coating or filler.

2. The term IND refers to the "Notice of Claimed Investigational Exemption for a New Drug."

3. Sponsor: The individual who takes responsibility for and initiates the clinical research project. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor is approved by the FDA.

4. Holder: An NIH individual, Institute, or NIH program such as NCI/CTEP, specifically designated by a sponsor to conduct a drug study is considered, in the Clinical Center, a holder. Holders report progress, adverse effects, proposed changes, and the like to the sponsor who, in turn, reports as required to the FDA.

5. Phase I Study: Phase I includes the initial introduction of an investigational new drug into humans. Phase I studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase I, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase II studies. The total number of subjects and patients included in Phase I studies varies with the drug, but is generally in the range of 20-80.

6. Phase II Study: Phase II includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase II studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

7. Phase III Study: Phase III studies are expanded controlled and uncontrolled trials. There are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug, and to provide an adequate basis for physical labeling. Phase III studies usually include from several hundred to several thousand subjects.

8. Phase IV Study: Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain postmarketing (Phase IV) studies to delineate additional information about the drug's risks, benefits, and optional use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase II studies, use of the drug in other patient populations or other stages of the disease, or use of the drug over a longer period of time.

LEGAL REQUIREMENTS

1. Section 505(a) of the Federal Food, Drug, and Cosmetic Act prohibits any person from introducing any new drug into interstate commerce without approval.

2. Section 505(i) of the Act requires the Secretary of the Department of Health and Human Services to promulgate regulations for exempting from the requirement in paragraph 1 drugs intended solely for investigational use by experts whose scientific training and experience qualify them to investigate the safety and effectiveness of those drugs.

3. The regulations governing investigational drugs are codified at 21 CFR 312. These regulations require the filing of a "Notice of Claimed Investigational Exemption for a New Drug," IND, before starting any research project involving investigational drugs. Investigators may contact the Protocol Coordination Service Center (PCSC) for assistance to obtain a copy of 21 CFR 312.

FILING AN IND

1. It is the responsibility of the principal investigator to recognize when a proposed use of a drug requires filing of an IND with the FDA. Investigators uncertain of the current status of the drug should contact the Pharmaceutical Development Service of the Clinical Center Pharmacy Department.

2. It is the responsibility of the Institutional Review Board (IRB) to certify whether a drug research study requires the filing of an IND.

3. A would-be NIH sponsor must file a written request for an IND approval with the FDA. The Clinical Center Pharmacy Department provides assistance to investigators in addressing FDA requirements, obtaining required IND submission forms, and identifying points of contact at the FDA. In addition, they: assist in investigational drug management and accountability, returning unused portions of the drugs to the drug sponsor; maintain study codes for blind studies; and work with investigators to unblind study codes when necessary. The sponsor may contact the PCSC for assistance with the application process.

   The following items must be submitted for FDA approval:

   a. Clinical research protocol.
   b. A curriculum vitae and bibliography of each physician.
   c. Signed “Statement of Investigator,” Form FD-1572 (if study is Phase I or II).
   d. Signed “Investigational New Drug Application,” Form FD-1571.
   e. Manufacturing information:
      (1) For marketed drugs that are unaltered prior to use, provide:
         (a) Source of drug (name and address of manufacturer).
         (b) Dosage form and strength.
         (c) Copy of label as found on the marketed package.
      (2) For non-marketed drugs and chemicals supplied to the investigator by a manufacturer, provide:
         (a) Source of drug (name and address of manufacturer).
         (b) Dosage form and strength.
         (c) Copy of label as found on package.
         (d) A letter from the manufacturer to the FDA authorizing that agency to use the manufacturing information provided by the manufacturer in its other submissions.

(3) For drugs altered by or prepared completely by the CC Pharmaceutical Development Service, PDS provides analytical data sheets for the active drug(s) and the finished dosage form(s). The data include:

(a) Best available descriptive name (including the chemical formula, if known) of the new drug substance and a statement of how it is to be administered.

(b) Source of the new drug, including name and address of supplier.

(c) Brief description of the preparation of the new drug and the methods used to determine its identify, purity, and potency, adequate for the purpose and period of clinical trial.

(d) If inactive ingredients are used, these should be listed together with a statement concerning their quality, i.e., USP or NF grade.

(e) A statement of the quantitative composition (including inactive ingredients) of the finished dosage form, a brief description of the preparation of the finished dosage form, methods of analysis, and results obtained on each batch.

(f) A copy of the label to be used on the bottle, box, ampule, etc.

4. If the sponsor is a pharmaceutical firm, the investigator is required to provide to the sponsor (and not the FDA) the following information:

   a. Clinical research protocol.
   b. A curriculum vitae and bibliography of each physician participating in the study.
   c. Signed "Statement of Investigator" Form FD-1572 (if study is Phase I or II).

5. NIH sponsors are to file directly with the FDA. The FDA requires all documentation in triplicate. In addition, one copy should be forwarded to the Protocol Coordination Service Center (PCSC), Medical Record Department, CC (Building 10, Room 1S231B).

6. Protocols of NIH sponsors must be assessed by the FDA and by an IRB review:

   a. It is the responsibility of the NIH sponsors to provide to the PCSC a copy of the letter requesting the IND exemption and a copy of the FDA receipt-acknowledgment letter bearing the new IND number.

   b. Only when the protocol file is complete (IRB approval, compliance with IRB stipulations, IND receipt notification, and radiation approval, where appropriate) will the protocol be submitted by the PCSC to the Director, Clinical Center, for final approval.

c. Following approval by the Director, CC, the investigator may begin work on the protocol 30 days after the date of the FDA receipt-acknowledgment letter. The PCSC will notify the Principal Investigator upon protocol approval by the Director, CC.

The PCSC will forward the complete copy of the approved protocol, and copies of all subsequent amendments to the protocol, to the Clinical Center Pharmacy Department.

CONDUCT OF AN INVESTIGATION

1. Drug disposition records are required:

   a. The Pharmacy Department, Clinical Center, will be responsible for the storage and issuance of all drugs intended for patient use. All drugs that the investigator receives directly from a pharmaceutical company must be submitted to the Pharmaceutical Development Service, Pharmacy Department (Building 10, Room 1D-35), for identification and registration.

   b. Physicians and nurses will not administer investigational drugs unless there is an investigational new drug label and Pharmacy Department-assigned control number attached to the product.

   c. FDA regulations prohibit the distribution of investigational drugs to investigators not identified in the IND application or its amendments.

2. Progress reports to the FDA are required of IND sponsors at intervals not to exceed one year. Investigators may include the annual report information required in 21 CFR 312.33 as part of the protocol's continuing review, submitting one document to the FDA and IRB.

   The Clinical Center Pharmacy Department will assist the IND sponsor in the preparation of the progress report upon request.

   a. Sponsors, whether NIH or pharmaceutical firm, should file directly with the FDA. One copy of each report should be forwarded to the PCSC at the time of the next protocol continuing review.

   b. The progress report required of NIH sponsors includes:

      (1) Name of the Institute.
      (2) Clinical project number assigned by the PCSC.
      (3) Name of the drug or drugs.
      (4) Investigational New Drug Number assigned by the FDA.

(5) A brief narrative description of the research results since the last report including the numbers of patients (or normal volunteers) who received the drug and the nature of any untoward reactions.
(6) Any changes in the protocol or investigators.
(7) A statement of whether the project has been discontinued and, if it has, the reason(s) for discontinuance.
(8) Signature of the Principal Investigator.
(9) Signature of the Clinical Director.
(10) Date of the report.

3. Any adverse effect regarded as caused by, or probably caused by, the new drug should be the subject of an adverse reaction report. It is the Principal Investigator's responsibility to report any adverse effects to the following:

a. The Clinical Center Pharmacy.
b. The IND sponsor if other than the investigator.
c. The FDA (if the drug has an NIH sponsor).
d. The Institution Review Board that approved the protocol.
e. The PCSC (at the time of the protocol's next continuing review).

If the adverse effect is alarming, it must be reported immediately.

All adverse reactions are to be reviewed by the Institutional Review Board that last approved the project. If, in the opinion of the IRB, the effects or information are of sufficient moment, the protocol may be terminated, or an amendment prepared for review requesting (a) continued approval, or (b) approval of amended procedure(s) or subject populations.

4. Final reports are usually made in the medical literature and should be provided to the FDA with the last annual report.

The Clinical Center Pharmacy Department will assist the IND sponsor in the preparation of the final report upon request.

When a study is not started or is discontinued, the FDA must be notified. This notification should include the reason, assurance that all investigators associated with the project have been notified, and steps taken with respect to unused supplies of the drug.

All reports should be submitted by the IND sponsor with a copy forwarded to the PCSC.